



General

Guideline Title

Clinical Pharmacogenetics Implementation Consortium guidelines for cytochrome P450 2D6 genotype and codeine therapy: 2014 update.

Bibliographic Source(s)

Crews KR, Gaedigk A, Dunnenberger HM, Leeder JS, Klein TE, Caudle KE, Haidar CE, Shen DD, Callaghan JT, Sadhasivam S, Prows CA, Kharasch ED, Skaar TC. Clinical Pharmacogenetics Implementation Consortium guidelines for cytochrome P450 2D6 genotype and codeine therapy: 2014 update. Clin Pharmacol Ther. 2014 Apr;95(4):376-82. [40 references] [PubMed](#)

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Crews KR, Gaedigk A, Dunnenberger HM, Klein TE, Shen DD, Callaghan JT, Kharasch ED, Skaar TC, Clinical Pharmacogenetics Implementation Consortium. Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for codeine therapy in the context of cytochrome P450 2D6 (CYP2D6) genotype. Clin Pharmacol Ther. 2012 Feb;91(2):321-6. [40 references]

Regulatory Alert

FDA Warning/Regulatory Alert

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- [August 31, 2016 – Opioid pain and cough medicines combined with benzodiazepines](#) : A U.S. Food and Drug Administration (FDA) review has found that the growing combined use of opioid medicines with benzodiazepines or other drugs that depress the central nervous system (CNS) has resulted in serious side effects, including slowed or difficult breathing and deaths. FDA is adding Boxed Warnings to the drug labeling of prescription opioid pain and prescription opioid cough medicines and benzodiazepines.
- [March 22, 2016 – Opioid pain medicines](#) : The U.S. Food and Drug Administration (FDA) is warning about several safety issues with the entire class of opioid pain medicines. These safety risks are potentially harmful interactions with numerous other medications, problems with the adrenal glands, and decreased sex hormone levels. They are requiring changes to the labels of all opioid drugs to warn about these risks.

Recommendations

Major Recommendations

The strength of therapeutic recommendations (Strong, Moderate, Optional) is defined at the end of the "Major Recommendations" field.

Gene: *CYP2D6*

Genetic Test Interpretation

Most clinical laboratories report cytochrome P450 2D6 (*CYP2D6*) genotype using the star (*) allele nomenclature and may provide interpretation of the patient's predicted metabolizer phenotype. Single-nucleotide polymorphisms (SNPs) and other sequence variations, including insertions and deletions, are determined by genetic laboratory tests. The reference SNP number (rs number) for a SNP defines the specific genomic nucleotide alteration. Each star (*) allele (or haplotype) is defined by the presence of a specific combination of SNPs and/or other sequence alterations within the *CYP2D6* gene locus. The key alleles with their allele-defining SNPs and respective impacts on *CYP2D6* enzyme function are provided in Supplementary Table S2 online (see the "Availability of Companion Documents" field). Genetic results are reported as a diplotype, which includes one maternal and one paternal allele (e.g., *CYP2D6**1/*4). In some cases, patients have more than two copies of the *CYP2D6* gene; up to 13 gene copies have been described. Those alleles are denoted by an "xN" following the allele designation (e.g., *CYP2D6**2x2 duplication; see Supplementary Data online for details [see the "Availability of Companion Documents" field]). Additional details about allele nomenclature and definitions can be found at <http://www.cypalleles.ki.se/cyp2d6.htm> [redacted], and information regarding the effects of allelic variation on *CYP2D6* substrates can be found at the Pharmacogenomics Knowledgebase (<http://www.pharmgkb.org/search/annotatedGene/cyp2d6/haplotype.jsp> [redacted]). *CYP2D6* allele frequencies differ substantially among racial and ethnic groups. Supplementary Table S1 online summarizes the most important frequencies for various ethnic groups (see the "Availability of Companion Documents" field).

The combination of alleles is used to determine a patient's diplotype. *CYP2D6* alleles are characterized as wild-type (normal function), reduced-function, or nonfunctional alleles based on the expected activity of the enzyme that they encode. Each allele is assigned an activity value (i.e., 0 for nonfunctional, 0.5 for reduced-function, or 1.0 for fully functional forms). Supplementary Tables S3 and S4 online (see the "Availability of Companion Documents" field) describe the activity score values assigned to selected alleles and example diplotypes, respectively. If multiple copies of the *CYP2D6* gene are detected, the activity score is multiplied by the number of copies of each allele present. The total *CYP2D6* activity score is the sum of the values assigned to each allele, which typically ranges from 0 to 3.0 but may exceed 3.0 in rare cases.

The *CYP2D6* activity score relates to the phenotype classification system as follows (Table 1 below): patients with an activity score of 0 are poor metabolizers, those with a score of 0.5 are considered intermediate metabolizers, and those with a score of 1.0, 1.5, or 2.0 represent a range of extensive metabolizers. Patients with a score >2.0 are classified as ultrarapid metabolizers. The extensive metabolizer phenotype represents normal (wild-type) enzyme activity. The incidence of poor and ultrarapid metabolizers varies greatly among populations (0–10% and 0–29%, respectively). Predicted phenotypes of common diplotypes are summarized in Supplementary Table S5 online (see the "Availability of Companion Documents" field).

Subjects with genotypes giving rise to an activity score of 1.0, which can be due to a diplotype containing one functional and one nonfunctional allele or containing two reduced-function alleles, are classified by some investigators as intermediate metabolizers. Regardless of the term used to describe such individuals (extensive or intermediate metabolizer), their *CYP2D6* activity is lower as compared with subjects having two fully functional alleles (with an activity score of 2.0) and higher as compared with subjects having one reduced and one nonfunctional allele (with an activity score of 0.5). Because there is no gold standard for phenotype classification, genotypes that result in *CYP2D6* activity scores of 1.0, 1.5, and 2.0 are grouped together as extensive metabolizers in this guideline based on data specific for codeine metabolism (Supplementary Table S6 online [see the "Availability of Companion Documents" field]).

Reference laboratories providing clinical *CYP2D6* genotyping may use varying methods to assign phenotypes. Therefore, it is advisable to note a patient's *CYP2D6* diplotype and to calculate an activity score before making therapeutic decisions about codeine therapy.

Table 1. Assignment of Likely Codeine Metabolism Phenotypes Based on Cytochrome P450 2D6 (*CYP2D6*) Diplotypes

Likely Phenotype ^a	Activity Score	Genotypes	Examples of Diplotypes
Ultrarapid metabolizer (~1–2% of patients)	>2.0	An individual carrying more than two copies of functional alleles	*1/*1xN, *1/*2xN
Extensive metabolizer	1.0–2.0 ^b	An individual carrying two alleles encoding full or reduced function; or one full-function allele together with either one nonfunctional or one reduced-function allele	*1/*1, *1/*2, *2/*2, *1/*41, *1/*4, *2/*5,

Likely Phenotype ^a	Activity Score	Genotypes	Examples of Diplotypes
Intermediate metabolizer (~2–11% of patients)	0.5 ^b	An individual carrying one reduced-function and one nonfunctional allele	*1/*10, *5/*41
Poor metabolizer (~5–10% of patients)	0	An individual carrying no functional alleles	*4/*4, *4/*5, *5/*5, *4/*6

^aThe frequency estimates are based on data from Caucasians and may differ substantially for other ethnicities. See Supplementary Data online (see the "Availability of Companion Documents" field) for estimates of phenotype frequencies among different ethnic/geographic groups.

^bNote that some investigators define patients with an activity score of 0.5 and 1.0 as intermediate metabolizers and those with an activity score of 1.5 and 2.0 as extensive metabolizers. Classifying patients with an activity score of 1.0 as extensive metabolizers in this guideline is based on data specific for formation of morphine from codeine in these patients.

Drug: Codeine

Therapeutic Recommendation

Table 2 below summarizes the therapeutic recommendations for codeine based on *CYP2D6* phenotype. A standard starting dose of codeine, as recommended in the product label, is warranted in patients with an extensive metabolizer phenotype (i.e., a *CYP2D6* activity score of 1.0–2.0). Likewise, a standard starting dose of codeine is warranted in patients with an intermediate metabolizer phenotype (i.e., activity score of 0.5); these patients should be monitored closely for less-than-optimal response and should be offered an alternative analgesic if warranted. If the *CYP2D6* substrate tramadol is selected as alternative therapy in intermediate metabolizers, therapy should be monitored closely due to the possibility of poor response.

If clinical genotyping identifies a patient as a *CYP2D6* poor metabolizer (i.e., activity score of 0), current evidence supports the avoidance of codeine and the use of an alternative analgesic due to the possibility of lack of effect. Use of an analgesic other than the *CYP2D6* substrates tramadol, hydrocodone, or oxycodone in poor metabolizers may be preferable. There is insufficient evidence in the literature to recommend a higher dose of codeine in poor metabolizers, especially considering the evidence that select adverse effects do not differ between poor and extensive metabolizers. In a patient identified as a *CYP2D6* ultrarapid metabolizer (i.e., activity score of >2.0), the choice of another analgesic should be made to avoid the risk of severe toxicity with a "normal" dose of codeine.

To avoid treatment complications, opioids that are not metabolized by *CYP2D6*, including morphine, oxymorphone, buprenorphine, fentanyl, methadone, and hydromorphone, along with nonopioid analgesics, may be considered as alternatives for use in *CYP2D6* poor metabolizers and ultrarapid metabolizers based on the type, severity, and chronicity of the pain being treated.

Table 2. Codeine Therapy Recommendations Based on Cytochrome P450 2D6 (*CYP2D6*) Phenotype

Phenotype	Implications for Codeine Metabolism	Recommendations for Codeine Therapy	Classification of Recommendation for Codeine Therapy ^a	Consideration for Alternative Opioids
Ultrarapid Metabolizer	Increased formation of morphine following codeine administration, leading to higher risk of toxicity	Avoid codeine use due to potential for toxicity.	Strong	Alternatives that are not affected by this <i>CYP2D6</i> phenotype include morphine and nonopioid analgesics. Tramadol and, to a lesser extent, hydrocodone and oxycodone are not good alternatives because their metabolism is affected by <i>CYP2D6</i> activity. ^{b,c}
Extensive Metabolizer	Normal morphine formation	Use label-recommended age- or weight-specific dosing.	Strong	—
Intermediate Metabolizer	Reduced morphine formation	Use label-recommended age- or weight-specific dosing. If no response, consider alternative	Moderate	Monitor tramadol use for response.

Phenotype	Implications for Codeine Metabolism	Recommendations for Codeine Therapy	Classification of Recommendation for Codeine Therapy ^a	Consideration for Alternative Opioids
Poor Metabolizer	Greatly reduced morphine formation following codeine administration, leading to insufficient pain relief	Avoid codeine use due to lack of efficacy.		Alternatives that are not affected by this <i>CYP2D6</i> phenotype include morphine and nonopioid analgesics. Tramadol and, to a lesser extent, hydrocodone and oxycodone are not good alternatives because their metabolism is affected by CYP2D6 activity; these agents should be avoided. ^{b,c}

^aRating scheme is described in the "Rating Scheme for the Strength of the Recommendations" field.

^bThere is substantial evidence for decreased efficacy of tramadol in poor metabolizers and a single case report of toxicity in an ultrarapid metabolizer with renal impairment following tramadol use postsurgery. Use of other analgesics in *CYP2D6* poor and ultrarapid metabolizers may therefore be preferable.

^cSome other opioid analgesics, such as hydrocodone and oxycodone, are metabolized by *CYP2D6*. To avoid treatment complications, opioids that are not metabolized by *CYP2D6*, including morphine, oxymorphone, buprenorphine, fentanyl, methadone, and hydromorphone, along with nonopioid analgesics, may be considered as alternatives for use in *CYP2D6* poor and ultrarapid metabolizers.

Definitions:

Strength of Therapeutic Recommendations

Strong: The evidence is high quality and the desirable effects clearly outweigh the undesirable effects.

Moderate: There is a close or uncertain balance as to whether the evidence is high quality and the desirable clearly outweigh the undesirable effects.

Optional: The desirable effects are closely balanced with undesirable effects and there is room for differences in opinion as to the need for the recommended course of action.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Pain

Guideline Category

Prevention

Risk Assessment

Treatment

Clinical Specialty

Medical Genetics

Pharmacology

Intended Users

Advanced Practice Nurses

Pharmacists

Physician Assistants

Physicians

Guideline Objective(s)

- To update the 2012 Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for cytochrome P450 2D6 (*CYP2D6*) genotype and codeine therapy
- To summarize evidence from the literature supporting the association between *CYP2D6* genotype and codeine metabolism and provide therapeutic recommendations for codeine based on *CYP2D6* genotype

Target Population

Patients with pain requiring analgesics

Interventions and Practices Considered

Dosing of codeine therapy based on cytochrome P450 2D6 (*CYP2D6*) genotype

Major Outcomes Considered

- Level of codeine analgesia
- Rate of morphine formation
- Risk of toxicity
- Adverse drug reactions

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

The guideline developers searched the PubMed® database (1966 to August 2013) and Ovid MEDLINE (1950 to August 2013) for keywords (cytochrome P450 2D6) OR (*CYP2D6*) AND (codeine OR morphine) for the association between *CYP2D6* genotype and codeine metabolism or codeine-related adverse drug event (ADE) or outcome. For additional reviews, see references in the original guideline document.

To construct a *CYP2D6* minor allele frequency table based on ethnicity, the PubMed® database (1966 to August 2013) and Ovid MEDLINE (1950 to August 2013) were searched using the following criteria: ((*CYP2D6* or *2D6*) AND (genotype OR allele OR frequency OR minor allele OR variant OR ethnic OR race OR racial OR ethnicity)). Studies were considered for inclusion if: (1) the ethnicity of the population was clearly indicated, (2) either allele frequencies or minor allele percentages for *CYP2D6* genotypes were reported, (3) the method by which *CYP2D6* was

genotyped was reliable and proven (no proof-of-principle experiments), (4) the sample population consisted of at least 50 patients (with few exceptions), and (5) the study represented an original publication (no reviews or meta-analyses).

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Levels of Evidence

High: Evidence includes consistent results from well-designed, well-conducted studies.

Moderate: Evidence is sufficient to determine effects, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies; generalizability to routine practice; or indirect nature of the evidence.

Weak: Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information.

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

The Clinical Pharmacogenetics Implementation Consortium's (CPIC's) therapeutic recommendations are based on weighting the evidence from a combination of preclinical functional and clinical data. Some of the factors that are taken into account in evaluating the evidence supporting therapeutic recommendations include: *in vivo* pharmacokinetic and pharmacodynamic data for codeine, *in vitro* enzyme activity of tissues expressing wild-type or variant-containing *CYP2D6*, *in vitro* *CYP2D6* enzyme activity from tissues isolated from individuals of known *CYP2D6* genotypes, and *in vivo* pre-clinical and clinical pharmacokinetic and pharmacodynamic studies.

The evidence was graded using a scale (high, moderate or weak) based on previously published criteria and applied to other CPIC guidelines (see the "Rating Scheme for the Strength of the Evidence" field).

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Overall, the therapeutic recommendations are simplified to allow rapid interpretation by clinicians. The authors used a slight modification of a transparent and simple system for just three categories for recommendations adopted from the rating scale for evidence-based recommendations on the use of retroviral agents (<http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf>) (see the "Rating Scheme for the Strength of the Recommendations" field).

Rating Scheme for the Strength of the Recommendations

Strength of Therapeutic Recommendations

Strong: The evidence is high quality and the desirable effects clearly outweigh the undesirable effects.

Moderate: There is a close or uncertain balance as to whether the evidence is high quality and the desirable clearly outweigh the undesirable effects.

Optional: The desirable effects are closely balanced with undesirable effects and there is room for differences in opinion as to the need for the recommended course of action.

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

Peer Review

Description of Method of Guideline Validation

Not stated

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

The potential benefit of cytochrome P450 2D6 (*CYP2D6*) genotype testing is that patients with genotypes that confer a higher risk of ineffective analgesia or of an adverse event may be identified and an alternative analgesic may be administered.

Potential Harms

- Cytochrome P450 2D6 (*CYP2D6*) genotyping is reliable when performed in qualified laboratories. However, as with any laboratory test, a possible risk to the patient is an error in genotyping that could have long-term adverse health implications for the patient.
- Breastfeeding women with an ultrarapid metabolizer phenotype may achieve high serum concentrations of morphine on standard codeine therapy. This may lead to high levels of morphine in breast milk and dangerously high serum morphine levels in their breastfed infants. Caution should be used when prescribing codeine to a breastfeeding woman with an ultrarapid metabolizer status.
- In February 2013, the U.S. Food and Drug Administration (FDA) announced its strongest and new black box warning against codeine use to manage postoperative pain in children following tonsillectomy with or without adenoidectomy. This warning was in response to further FDA review of the codeine-related deaths and serious adverse drug reactions. The FDA warning is applicable to all children undergoing tonsillectomy with or without adenoidectomy irrespective of their obstructive sleep apnea status or *CYP2D6* genotype/phenotype.
- Common adverse reactions to codeine include nausea, vomiting, drowsiness, light-headedness, dizziness, sedation, shortness of breath, constipation, and itching. Serious adverse reactions include respiratory depression and, rarely, circulatory depression, respiratory arrest,

shock, and cardiac arrest.

- Pharmacokinetic studies show increased conversion of codeine to morphine in *CYP2D6* ultrarapid vs. extensive metabolizers, which can result in toxic systemic concentrations of morphine even at low codeine doses.

Qualifying Statements

Qualifying Statements

Caveats: Appropriate Use and/or Potential Misuse of Genetic Tests

Rare cytochrome P450 2D6 (*CYP2D6*) variants may not be included in the genotype test used, and patients with rare variants may be assigned a "wild-type" (*CYP2D6*1*) genotype by default. Thus, an assigned "wild-type" allele may, in rare cases, harbor a loss-of-function variant resulting in inadequate pain response to codeine. Like all diagnostic tests, that for *CYP2D6* genotype is one of multiple pieces of information that clinicians should consider in guiding their therapeutic choice for each patient. Furthermore, there are several other factors that cause potential uncertainty in the genotyping results and phenotype predictions. These are discussed in detail in the Supplementary Data online (see the "Availability of Companion Documents" field).

Disclaimer

Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines reflect expert consensus based on clinical evidence and peer-reviewed literature available at the time they are written and are intended only to assist clinicians in decision making and to identify questions for further research. New evidence may have emerged since the time a guideline was submitted for publication. Guidelines are limited in scope and are not applicable to interventions or diseases not specifically identified. Guidelines do not account for all individual variations among patients and cannot be considered inclusive of all proper methods of care or exclusive of other treatments. It remains the responsibility of the health-care provider to determine the best course of treatment for a patient. Adherence to any guideline is voluntary, with the ultimate determination regarding its application to be made solely by the clinician and the patient. CPIC assumes no responsibility for any injury to persons or damage to persons or property arising out of or related to any use of CPIC's guidelines, or for any errors or omissions.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Clinical Algorithm

Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Living with Illness

Staying Healthy

IOM Domain

Effectiveness

Safety

Identifying Information and Availability

Bibliographic Source(s)

Crews KR, Gaedigk A, Dunnenberger HM, Leeder JS, Klein TE, Caudle KE, Haidar CE, Shen DD, Callaghan JT, Sadhasivam S, Prows CA, Kharasch ED, Skaar TC. Clinical Pharmacogenetics Implementation Consortium guidelines for cytochrome P450 2D6 genotype and codeine therapy: 2014 update. Clin Pharmacol Ther. 2014 Apr;95(4):376-82. [40 references] [PubMed](#)

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2012 Feb (revised 2014 Apr)

Guideline Developer(s)

Clinical Pharmacogenetics Implementation Consortium - Independent Expert Panel

Source(s) of Funding

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Guideline Committee

Not stated

Composition of Group That Authored the Guideline

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Financial Disclosures/Conflicts of Interest

A.G. and K.R.C. each received compensation for services as an expert witness on a legal case involving codeine. The other authors declared no conflict of interest. The content of this article is solely the responsibility of the authors and does not necessarily represent the official views of the Agency for Healthcare Research and Quality.

Guideline Status

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Guideline Availability

Electronic copies: Available from the [Pharmacogenomics Knowledge Base Web site](#) .

Availability of Companion Documents

The following are available:

- Supplementary material, including tables and methodological information, is available from the [Pharmacogenomics Knowledgebase Web site](#) .
- A codeine and morphine pathway is also available from the [Pharmacogenomics Knowledgebase Web site](#) .
- An interactive dosing table is available from the [Pharmacogenomics Knowledgebase Web site](#) .
- "Look up" tables for *CYP2D6*, which contain phenotype and clinical support system information based on haplotypes and diplotypes, are available from the [Pharmacogenomics Knowledgebase Web site](#) .

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on May 15, 2013. The information was verified by the guideline developer on June 25, 2013. This summary was updated by ECRI Institute on July 9, 2014. The updated information was verified by the guideline developer on August 13, 2014. This summary was updated by ECRI Institute on June 2, 2016 following the U.S. Food and Drug Administration advisory on opioid pain medicines. This summary was updated by ECRI Institute on October 21, 2016 following the U.S. Food and Drug Administration advisory on opioid pain and cough medicines combined with benzodiazepines.

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